Quality of Life 3 and 12 Months Following Acute Pulmonary Embolism: Analysis From a Prospective Multicenter Cohort Study

Valerio, Luca ; Barco, Stefano ; Jankowski, Marius ; Rosenkranz, Stephan ; Lankeit, Mareike ; Held, Matthias ; et al

Abstract: BACKGROUND Few data are available on the long-term course and predictors of quality of life (QoL) following acute pulmonary embolism (PE). RESEARCH QUESTION What are the kinetics and determinants of disease-specific and generic health-related QoL 3 and 12 months following an acute PE? STUDY DESIGN AND METHODS The Follow-up after Acute Pulmonary Embolism (FOCUS) study prospectively followed up consecutive adult patients with objectively diagnosed PE. Patients were considered for study who completed the Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaire at predefined visits 3 and 12 months following PE. The course of disease-specific QoL as assessed using the PEmb-QoL and the impact of baseline characteristics using multivariable mixed effects linear regression were studied; also assessed was the course of generic QoL as evaluated by using the EuroQoL Group 5-Dimension 5-Level utility index and the EuroQoL Visual Analog Scale. RESULTS In 620 patients (44% women; median age, 62 years), overall disease-specific QoL improved from 3 to 12 months, with a decrease in the median PEmb-QoL score from 19.4% to 13.0% and a mean individual change of -4.3% (95% CI, -3.2 to -5.5). Female sex, cardiopulmonary disease, and higher BMI were associated with worse QoL at both 3 and 12 months. Over time, the association with BMI became weaker, whereas older age and previous VTE were associated with worsening QoL. Generic QoL also improved: the mean ± SD EuroQoL Group 5-Dimension 5-Level utility index increased from 0.85 ± 0.22 to 0.87 ± 0.20 and the visual analog scale from 72.9 ± 18.8 to 74.4 ± 19.1. INTERPRETATION In a large cohort of survivors of acute PE, the change of QoL was quantified between months 3 and 12 following diagnosis, and factors independently associated with lower QoL and slower recovery of QoL were identified. This information may facilitate the planning and interpretation of clinical trials assessing QoL and help guide patient management. CLINICAL TRIAL REGISTRATION German Clinical Trials Registry (Deutsches Register Klinischer Studien: www.drks.de); No.: DRKS00005939.

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CHEST

Quality of Life 3 and 12 Months Following Acute Pulmonary Embolism

Analysis From a Prospective Multicenter Cohort Study

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BACKGROUND: Few data are available on the long-term course and predictors of quality of life (QoL) following acute pulmonary embolism (PE).

RESEARCH QUESTION: What are the kinetics and determinants of disease-specific and generic health-related QoL 3 and 12 months following an acute PE?

STUDY DESIGN AND METHODS: The Follow-up after Acute Pulmonary Embolism (FOCUS) study prospectively followed up consecutive adult patients with objectively diagnosed PE. Patients were considered for study who completed the Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaire at predefined visits 3 and 12 months following PE. The course of disease-specific QoL as assessed using the PEmb-QoL and the impact of baseline characteristics using multivariable mixed effects linear regression were studied; also assessed was the course of generic QoL as evaluated by using the EuroQoL Group 5-Dimension 5-Level utility index and the EuroQoL Visual Analog Scale.

RESULTS: In 620 patients (44% women; median age, 62 years), overall disease-specific QoL improved from 3 to 12 months, with a decrease in the median PEmb-QoL score from 19.4% to 13.0% and a mean individual change of –4.3% (95% CI, –3.2 to –5.5). Female sex, cardiopulmonary disease, and higher BMI were associated with worse QoL at both 3 and 12 months. Over time, the association with BMI became weaker, whereas older age and previous VTE were associated with worsening QoL. Generic QoL also improved: the mean ± SD EuroQoL Group 5-Dimension 5-Level utility index increased from 0.85 ± 0.22 to 0.87 ± 0.20 and the visual analog scale from 72.9 ± 18.8 to 74.4 ± 19.1.

INTERPRETATION: In a large cohort of survivors of acute PE, the change of QoL was quantified between months 3 and 12 following diagnosis, and factors independently associated with lower QoL and slower recovery of QoL were identified. This information may facilitate the planning and interpretation of clinical trials assessing QoL and help guide patient management.

CLINICAL TRIAL REGISTRATION: German Clinical Trials Registry (Deutsches Register Klinischer Studien: www.drks.de); No.: DRKS00005939. CHEST 2021; 159(6):2428-2438

KEY WORDS: EQ-5D-5L; patient-centered outcomes; patient-reported outcomes; PeMB-QoL; pulmonary embolism; quality of life; VTE

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ABBREVIATIONS: EQ-5D-5L = EuroQoL Group 5-Dimension 5-Level; IQR = interquartile range; PE = pulmonary embolism; PEmb-QoL = Pulmonary Embolism Quality of Life; QoL = quality of life

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The annual incidence of acute pulmonary embolism (PE) continues to increase,[1-4] while early mortality related to this condition is progressively decreasing.[5-7] Consequently, and as many survivors report long-lasting and potentially severe symptoms or disability,[8] ensuring a good functional status and quality of life (QoL) over the long term following PE will present an important task for the years to come.

Take-home Points

Study Question: What are the kinetics and determinants of disease-specific and generic health-related QoL 3 and 12 months following an acute PE?

Results: Both disease-specific and generic health-related QoL improved between 3 and 12 months following an acute PE, with disease-specific QoL lower in women and those with higher BMI or pre-existing cardiopulmonary disease, and declining over time in older patients and those with a history of VTE.

Interpretation: Our data may be relevant to guide management and assess interventions in the context of a more comprehensive and holistic approach to patients recovering from acute PE.

Patient-centered outcomes such as self-reported health-related QoL form the basis of health care quality assessment,[9] and their inclusion as outcome measures in clinical trials is now recommended to guide shared decisions on health policy-making.[10] In the case of acute PE, assessment tools for generic (non-PE-specific) health-related QoL have been applied in registries and small-scale cohort studies of selected populations.[11,12] In addition, the Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaire was developed[13] and validated[14] as a disease-specific instrument to measure QoL in survivors of acute PE. Disease-specific instruments for the assessment of health-related QoL are a valuable addition to generic standardized tools to identify and monitor "quality dimensions" of concern and compare results across studies on patients with the same condition.[15] The application of PEmb-QoL in cross-sectional studies[16,17] and prospective cohort studies of selected populations[11] has generated the hypothesis that complete functional recovery, as reflected in several QoL dimensions, may require several months, or possibly not occur at all, thus adding further support to the clinical and epidemiologic relevance of the "post-PE syndrome."[18] However, to the best of our knowledge, neither the temporal course of QoL and its individual dimensions nor their association with baseline clinical characteristics have thus far been the object of investigation in prospectively studied large cohorts of survivors of acute PE.

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The Follow-up after Acute Pulmonary Embolism (FOCUS) study[19] is an ongoing prospective, observational, multicenter study systematically following up all-comers with symptomatic acute PE; follow-up comprises a standardized comprehensive program of clinical, echocardiographic, functional, and laboratory testing over a 2-year period. The aim of the current analysis was to dissect the indicators of disease-specific and generic health-related QoL at 3- and 12-month follow-up following the diagnosis of PE and to identify baseline characteristics that may predict persisting symptoms or functional limitation.

Study Design and Methods

Study Population

FOCUS (German Clinical Trials Registry number DRKS00005939) has included consecutive unselected patients with a confirmed diagnosis of acute symptomatic PE.[19] Patients were enrolled at 17 large-volume centers across Germany and are being followed up over a 2-year period with a predefined visit plan; the plan includes clinical, functional, laboratory, and echocardiographic examinations as well as health status assessments at five prespecified visits (upon enrollment, at hospital discharge, and at 3, 12, and 24 months). The study protocol does not mandate diagnostic or therapeutic decisions; patients are treated according to the standard of care at the participating centers and in adherence to current guidelines.[8,20] Patients with asymptomatic PE or previously diagnosed chronic thromboembolic pulmonary hypertension were excluded from the study.[19]

The current analysis included patients who had completed, as of March 2020, at least one item in all numeric dimensions of the 40-item PEmb-QoL questionnaire both at the 3-month and the 12-month visit.

Assessment of QoL

The PEmb-QoL questionnaire used in the current analysis was developed in 2009 to selectively measure disease-specific health-related QoL following PE.[14] The questionnaire was translated from the English version to German. The PEmb-QoL has been validated and shown to be a reliable disease-specific questionnaire for patients with PE.[17,21] It includes nine questions (e-Table 1). Seven of these questions assess health-related QoL, covering six numeric "dimensions": (1) frequency of complaints (question 1), (2) limitation of activities in daily life (question 4), (3) work-related problems (question 5), (4) social limitations (question 6), (5) intensity of complaints (questions 7 and 8), and (6) emotional complaints (question 9). The percentage scores obtained in each one of the six dimensions are averaged to obtain an overall percentage score (0-100), aiming to reflect the overall QoL. Of note, higher scores indicate worse QoL. Although the remaining two questions do not contribute to the overall score, they provide descriptive information on the time of day when the symptoms appear and the patient's perceived current cardiopulmonary function compared with 1 year earlier.[13]

Generic, nondisease-specific health-related QoL was assessed by using the EuroQoL Group 5-Dimension 5-Level (EQ-5D-5L) questionnaire and its corresponding visual analog scale.[22] The EQ-5D-5L assesses health-related QoL descriptively in five dimensions: (1) mobility, (2) self-care, (3) usual activities, (4) pain and discomfort, and (5) anxiety and depression. The information is integrated into an overall index that ranges from 0 to 1 and is calculated based on country-specific reference value sets. In this index, and in contrast to the PEmb-QoL score, higher values indicate better health. The EQ-5D-5L health index was calculated with the value set for Germany.

The EuroQol Visual Analogue Scale ranges from 0 to 100, with higher scores indicating better health.

Clinical Characteristics at Baseline

The clinical features at the time of index PE considered for association with QoL were selected based on their association with the course of generic indicators of QoL, or the PEmb-QoL, in previous studies.[11,12,23,24] They included sex, age, BMI, chronic heart or lung disease, cancer, previous VTE, smoking status, a major transient/reversible risk factor for the index PE event, and low-risk index PE. Chronic cardiopulmonary disease included chronic heart failure, coronary artery disease, or chronic pulmonary disease. Previous VTE was defined as history of deep lower extremity vein thrombosis, PE, or arm vein thrombosis. Major transient/reversible risk factors for index PE were defined as major surgery, trauma, or immobilization within 30 days preceding the diagnosis. Low-risk PE was defined as an episode not accompanied by hemodynamic instability, clinical, imaging, or laboratory indicators of acute right ventricular pressure overload and dysfunction, or serious comorbidity or any other condition that might adversely affect early prognosis.[20]

Statistical Methods

Categorical variables are presented as frequencies and percentages; continuous variables are presented as medians with first and third quartiles (interquartile range [IQR]), or means with the corresponding SD, according to their distribution. Mean differences with 95% CIs obtained from paired Student *t* tests (provided that the differences were normally distributed) were used to calculate intraindividual changes in overall and dimension-specific PEmb-QoL score, EQ-5D-5L utility index, and EuroQoL Visual Analogue Scale from 3 to 12 months; they were also used to study the univariate association between baseline clinical characteristics and changes in overall PEmb-QoL score from 3 to 12 months. A mixed effects model with random intercepts was used to investigate the association between baseline clinical characteristics and the overall PEmb-QoL score at 3 and 12 months. To evaluate whether the associations changed over time, the model included interaction terms between each clinical characteristic and time (defined as the two time points, 3 months [used as reference level] and 12 months). The proportion of patients attaining a minimal clinically important difference of 15 points in the overall PEmb-QoL score as derived from a relatively healthy population of patients with acute PE was also calculated.[25] Two-tailed P values $< .05$ were considered significant. R version 3.6.1 (R Foundation for Statistical Computing) with the tidyverse packages was used for data analysis.

TABLE 1] Baseline Characteristics of Study Patients (N = 620)

Variable	Value
Patient demographic characteristics	
Women, n/N (%)	272/620 (44)
Age, median (IQR), y	62 (49-73)
White ethnicity, n/N (%)	613/620 (99)
Vital signs and other clinical parameters at diagnosis of pulmonary embolism[a]	
Systolic/diastolic BP, mean ± SD, mm Hg	136.7 ± 21.8/81.6 ± 13.2[a]
Heart rate, median (IQR), beats/min	87.5 (74.0-100.0)[a]
Oxygen saturation, median (IQR), %	96.0 (93.0-97.5)[a]
Respiratory rate, median (IQR), breaths/min	17 (15-20)[a]
Hemodynamic collapse, n/N (%)	16/620 (2.6)
Pulmonary embolism risk class,[b] n/N (%)	
Low risk	130/620 (21)
Intermediate risk	474/620 (76)
High risk	16/620 (2.6)
BMI, median (IQR), kg/m^2	28.3 (25.0, 32.3)
Glomerular filtration rate < 50 mL/min, n/N (%)	94/613 (15)
Risk factors for thrombosis and pulmonary embolism, n/N (%)	
Cancer or myeloproliferative disease	49/620 (7.9)
Estrogen-containing medications	51/620 (8.2)
Pregnancy or lactation	2/620 (0.3)
Recent long-distance travel	58/620 (9.4)
Recent surgery or trauma (last 30 d)	79/620 (13)
Recent immobilization	105/620 (17)
History of VTE	133/620 (21)
Comorbidities and other risk factors, n/N (%)	
Chronic pulmonary disease	78/620 (13)
Heart failure	25/620 (4.0)
Coronary artery disease	47/620 (7.6)
Arterial hypertension	324/620 (52)
Diabetes mellitus	64/620 (10)
Chronic liver disease	17/620 (2.7)
Chronic inflammatory disease	58/620 (9.4)
Smoking	101/620 (16)

IQR = interquartile range.
[a]Systolic BP values were available in 593 of 620 patients, diastolic BP in 590/620 patients, heart rate in 594 of 620 patients, oxygen saturation in 517 of 620 patients, respiratory rate in 399 of 620 patients, BMI in 615 of 620 patients, and glomerular filtration rate in 613 of 620 patients.
[b]Based on the 2019 Guidelines of the European Society of Cardiology.[8]

Results

Study Population

The current analysis focused on 620 patients who completed the PEmb-QoL questionnaire at both the 3- and the 12-month follow-up visit of the 799 patients with complete follow-up until 12 months. The median age of patients included in the analysis was 62 years (IQR, 49-73 years), and 43.9% were women (Table 1). The index PE followed a major transient risk factor in 141 (22.7%) patients and was classified as low risk in 130 (21.0%) patients. Comparison of the baseline characteristics of the study patients with a complete PEmb-QoL assessment vs without (n = 179) (e-Table 2) revealed no relevant differences.

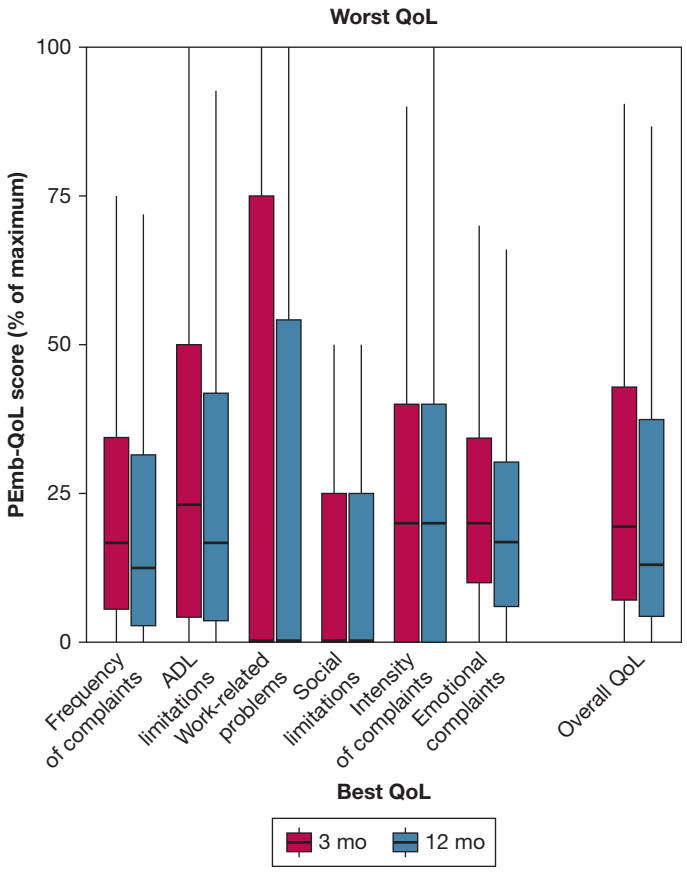

Figure 1 – *Distribution of dimension-specific and overall QoL as assessed by the PEmb-QoL score at 3 and 12 months. Tukey box plots depict the median and interquartile range of dimension-specific and overall QoL as percentage of the maximum PEmb-QoL score. Values obtained at 3-month (red boxes) and 12-month (blue boxes) follow-up following the diagnosis of PE are compared for a total of 620 patients. Higher PEmb-QoL scores indicate lower QoL; accordingly, "lower" blue box plots compared with the red ones indicate an improvement in QoL for the respective dimension (or the overall score) between month 3 and month 12. ADL = activities of daily living; PEmb-QoL = Pulmonary Embolism Quality of Life; QoL = quality of life.*

Disease-Specific Health-Related QoL

The distribution of the overall and dimension-specific PEmb-QoL scores at 3 and 12 months is depicted in Figure 1. The overall score decreased from a median of 19.4% (IQR, 7.1%-42.9%) to a median of 13.0% (IQR, 4.3%-37.4%). Because higher PEmb-QoL scores reflect worse QoL and lower scores reflect better QoL, this decrease indicated an overall improvement in QoL. The mean intraindividual change in overall QoL between the 3- and 12-month follow-up was –4.3% (95% CI, –3.2 to –5.5). The mean intraindividual change of the dimension-specific PEmb-QoL is shown in Figure 2; an improved QoL was observed in all six dimensions. When applying a proposed estimate for minimal clinically important difference of the PEmb-QoL score, a clinically important improvement was observed in 118 of 620 (19.0%) patients and a clinically important deterioration in 48 of 620 (7.7%) patients.

The descriptive question "at what time of the day are your lung symptoms most intense?" was answered by 567 patients at both follow-up visits. At both 3 and 12 months, the most commonly reported response was "never" (302 [53.3%] and 325 [57.3%] patients, respectively), followed by "any time of the day" (77 [16.4%] and 95 [16.8%] patients). The descriptive question "compared with 1 year ago, how would you rate the condition of your lungs in general now?" was answered by 585 patients at both 3 and 12 months; the distribution of the responses is displayed in Figure 3. At 3 months, the most common response was "much worse" or "somewhat worse" (201 [34.4%] patients), followed by "about the same" (175 [29.9%]) and "much better" or "somewhat better" (152 [26.0%]). Conversely, at 12 months the most common response was "much better" or "somewhat better" (324 [55.4%]), followed by "I do not have any problems" (119 patients [20.3%]).

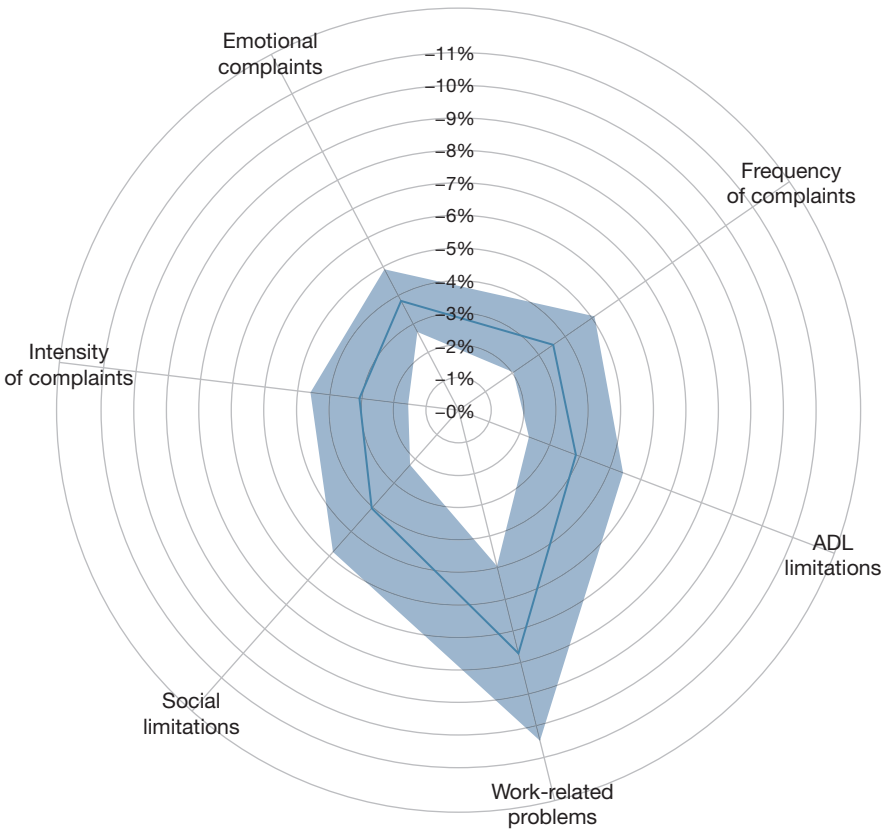

Figure 2 – *Intraindividual change in quality of life as assessed by using the Pulmonary Embolism Quality of Life (PEmbQoL) score between 3- and 12-month follow-up. The dark blue line (mean value) and the blue ribbon (corresponding 95% CI) indicate the intraindividual change in the PEmbQoL score between month 12 and month 3 of follow-up. They are plotted as a hexagon to represent each one of the six PEmb-QoL dimensions. Means and CIs were calculated by using paired two-sided Student t tests. For each dimension, the scale from 0% to –11% indicates the observed absolute difference in score percentage points between 12 and 3 months. A negative difference indicates improvement in quality of life between the 3-month and 12-month follow-up. ADL = activities of daily living.*

Baseline Characteristics and QoL Course

We performed a multivariable mixed effects regression analysis to investigate the independent association between characteristics at the time of PE diagnosis and overall disease-specific QoL (PEmb-QoL) during follow-up (n = 615; five patients with missing data on BMI); the results are summarized in Table 2. At both time points, QoL was worse in women, patients with a higher BMI, and patients with preexisting cardiopulmonary disease. The interaction terms showed that older age and history of VTE at baseline were associated with worsening of QoL over time; conversely, the association of higher BMI with QoL became weaker over time.

For descriptive purposes, the change in overall and dimension-specific QoL from 3 to 12 months according to selected clinical characteristics at the time of PE upon univariate testing is reported in e-Figure 1.

Generic Health-Related QoL

The EQ-5D-5L analysis was conducted in a total of 597 patients with completed questionnaires at both visits. The mean EQ-5D-5L index was 0.85 ± 0.22 at the 3-month visit, which improved to 0.87 ± 0.20 at 12 months (paired Student *t* test, $P = .002$). The proportion of answers reporting "no problems" in any of the five dimensions of the EQ-5D-5L questionnaire increased from 63.2% at 3 months to 66.2% at 12 months, with the proportion of answers reporting problems of any severity decreasing (slight, from 19.6% to 18.4%; moderate, from 11.6% to 10.8%; severe, from 4.8% to 4.0%; and extreme, from 0.8% to 0.6%). Figure 4 shows the distribution of these changes across all five EQ-5D-5L dimensions. Finally, the EuroQol Visual Analogue Scale (available in 608 patients) increased from a mean of 72.9 ± 18.8 points to 74.4 ± 19.1 points (paired Student *t* test for difference, $P = .022$), also reflecting improved QoL.

Discussion

This analysis of the prospective FOCUS study provides an outline of the level and long-term course of health-related QoL, as estimated by using both the disease-specific questionnaire PEmb-QoL and the generic assessment tool EQ-5D-5L. Both disease-specific and generic QoL improved between 3 and 12 months following an acute PE. This improvement was observed for all dimensions of PEmb-QoL and of EQ-5D-5L, covering different areas of a patient's life, functional

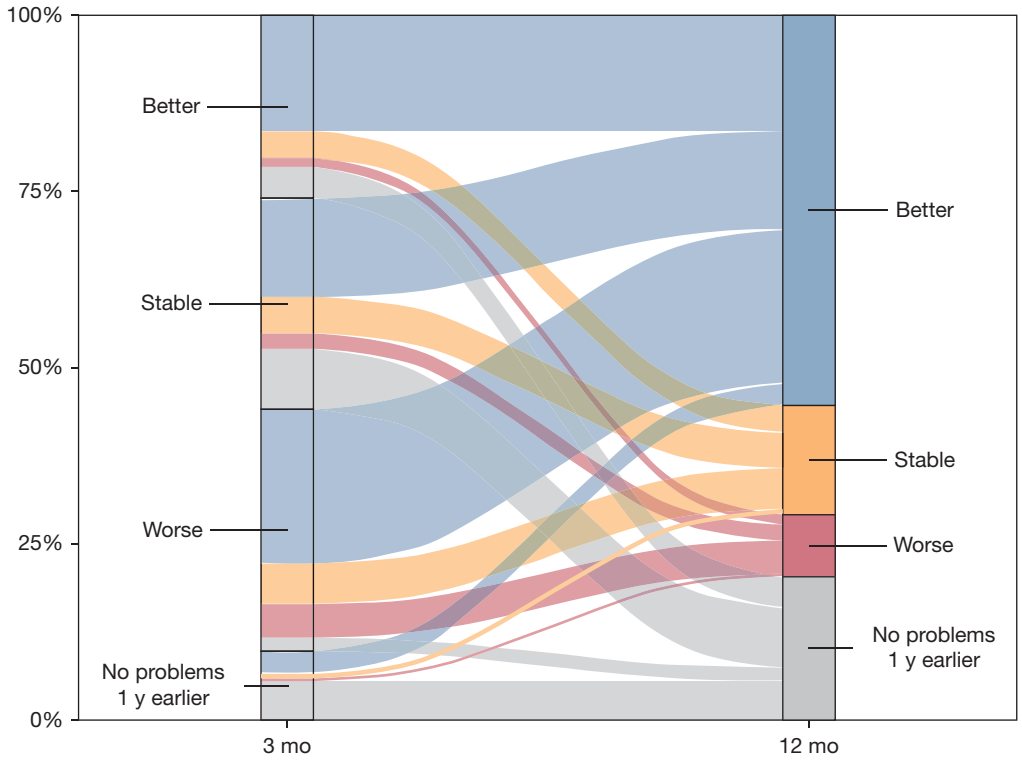

Figure 3 – *Perceived change in the patients' cardiopulmonary function at 3 and 12 months. Alluvial plot showing the percentage of each answer to question 3 of the Pulmonary Embolism Quality of Life (PEmb-QoL) score ("perceived change in cardiopulmonary function compared with 1 year earlier") in patients who answered the question at both visits (n = 585). Response at 3 months following the index PE refers to comparison with the condition 9 months prior to the index PE; response at 12 months refers to the comparison with the condition immediately prior to the index PE. "Worse" is defined as a response "much worse" or "somewhat worse"; "better," as a response "much better" or "somewhat better." "No problems 1 year earlier" corresponds to the response "I did not have any problems with my lungs" (e-Table 1).*

status, and symptoms. Female sex, higher BMI, and preexisting chronic cardiopulmonary disease were associated with worse QoL at both 3 and 12 months. Over time, the association with BMI became weaker, and QoL declined in older patients and those with a history of previous VTE.

In 620 patients enrolled in the ongoing multicenter FOCUS study who had survived the acute phase of PE, the mean individual improvement of overall disease-specific QoL between the 3- and 12-month follow-up following PE was 4.3 percentage points (95% CI, 3.2-5.5) in the PEmb-QoL questionnaire. This finding is considerably lower than the mean group improvement of 12.1 percentage points reported in the same follow-up period (from month 3 to month 12 following an acute PE) in a previous study on 100 patients at five Canadian hospitals.[11] This difference could be explained by the strict selection criteria of that study, which excluded patients with severe comorbidities, resulting in a low prevalence of potential contributors to a poor health status in the acute phase (at baseline). These include older age (mean age of 50 years vs 59.7 years of our study), previous VTE (excluded by Kahn et al[11]; present in 21.5% of the patients in our study), and smoking (7% vs 16.3% in our study).

Beyond the overall PEmb-QoL score, the time course of individual PEmb-QoL dimensions has not been previously studied. The validation study of PEmb-QoL reported the cross-sectional dimension-specific scores in 90 patients a median of 38 months (range, 10-91 months) following the index PE episode[14] and found a distribution of the dimension-specific scores similar to our findings at 12 months. This suggests that the scores in all individual dimensions and, consequently, the patient's "overall" disease-specific QoL may remain relatively stable in the first 12 months following an acute PE.

Previously reported associations between clinical characteristics at the time of the index PE and subsequent disease-specific QoL may not be directly comparable with our findings, as those studies included evaluation of QoL between hospital admission for the index event and 3 months thereafter. Such an approach

TABLE 2] Multivariable Mixed Effects Regression Analysis of the Association Between Clinical Characteristics at the Time of Index PE and Overall Disease-Specific Quality of Life at 3 and 12 Months

Characteristic	β (95% CI)
Time (12 mo vs 3 mo)	−7.4 (−15.2, 0.4)
Women (vs men)	7.9[b] (3.3, 12.6)
Age (per 10-y increase)	−0.1 (−1.6, 1.5)
BMI (per kg/m^2 increase)	0.8[b] (0.4, 1.2)
Chronic cardiopulmonary disease	9.6[b] (3.5, 15.6)
Cancer	3.3 (−5.4, 12.1)
Previous VTE	−4.5 (−10.1, 1.2)
Smoking	0.3 (−6.2, 6.8)
Major surgery, trauma, or immobilization[a]	−0.8 (−6.4, 4.8)
Low-risk (vs intermediate- or high-risk) index PE	3.1 (−2.9, 9.0)
Women × time	0.5 (−1.8, 2.9)
Age (per 10-y increase) × time	1.0[b] (0.5, 2.0)
BMI × time	−0.2[b] (−0.4, −0.03)
Chronic cardiopulmonary disease × time	1.4 (−1.6, 4.5)
Cancer × time	−2.0 (−6.4, 2.4)
Previous VTE × time	3.0[b] (0.2, 5.9)
Smoking × time	3.1 (−0.1, 6.4)
Major surgery, trauma, or immobilization × time	1.5 (−1.3, 4.3)
Low-risk index PE × time	0.5 (−2.5, 3.6)

The analysis was conducted on 615 patients with available data. Positive coefficients (95% CI) indicate worse overall disease-specific quality of life as estimated by the Pulmonary Embolism Quality of Life score compared with the reference level for each variable. In the interaction terms, time consists of the two time points (3 months [reference level] and 12 months), with positive coefficients indicating that the corresponding variable is associated with worsening quality of life over time. PE = pulmonary embolism.

[a]Within the 30 days preceding the diagnosis.

[b]$P < .05$.

may lead to QoL estimates more strongly affected by the early course of the disease and specific circumstances related to acute-phase treatment of the index event (eg, admission to an ICU, hospitalization in a general ward, early discharge). For example, the study by Kahn et al[11] reported an association of female sex and higher BMI, but not of lung disease or smoking status, with worse QoL following PE. It is likely that these latter associations were "diluted" by the inclusion of the QoL measurement at baseline or 1 month and may not become apparent until after the first 3 months, as was the case in the current study.

In the same context, it should be noted we found no association between the PE risk class in the acute phase[8] and QoL at follow-up. This fact supports the notion that risk stratification is important to assess only the early prognosis of acute PE, and it may also suggest that the deconditioning often observed in the long-term follow-up of PE can occur regardless of the initial PE severity, if the patient does not (or cannot) resume a healthy lifestyle.[26,27] We also found no association between active cancer at baseline and either the level of disease-specific QoL or its change over time. This finding is consistent with previous cross-sectional analyses that applied the PEmb-QoL score to smaller populations,[14,16,17] and it may reflect, among others, the fact that patients with advanced cancer are (understandably) underrepresented in studies focusing on long-term QoL.

In the current analysis, the course of generic, nondisease-specific health-related QoL from 3 to 12 months as assessed by using the EQ-5D-5L utility index and the EuroQol Visual Analog Scale substantially paralleled the improvement observed in disease-specific QoL. This improvement encompassed all EQ-5D-5L dimensions with the exception of "self-care," which displayed a lower burden than the other dimensions already at the 3-month follow-up. In a previous analysis of multicountry prospective registry data, the course of the EQ-5D-5L utility index was comparable to our findings, whereas its absolute levels differed according to country; those observed in German-speaking countries were similar to those we report.[12]

Our findings may have direct implications for clinical practice and future research. Following management decisions after risk stratification of acute PE, the first follow-up evaluation at 3 months represents a critical milestone for decisions regarding the duration of anticoagulation and possible additional testing for late sequelae of PE.[8,28] We provide the first estimate of clinically important deterioration of disease-specific QoL from 3 to 12 months (7.7% of the patients in the study cohort). Although based on an estimate of minimal clinically important change derived in relatively healthy patients with acute PE, the generalizability of which needs confirmation, this deterioration may provide the basis of a clinical tool to identify patients who are experiencing late PE sequelae in a standardized way. The associations between baseline characteristic and subsequent course of QoL that were identified in the

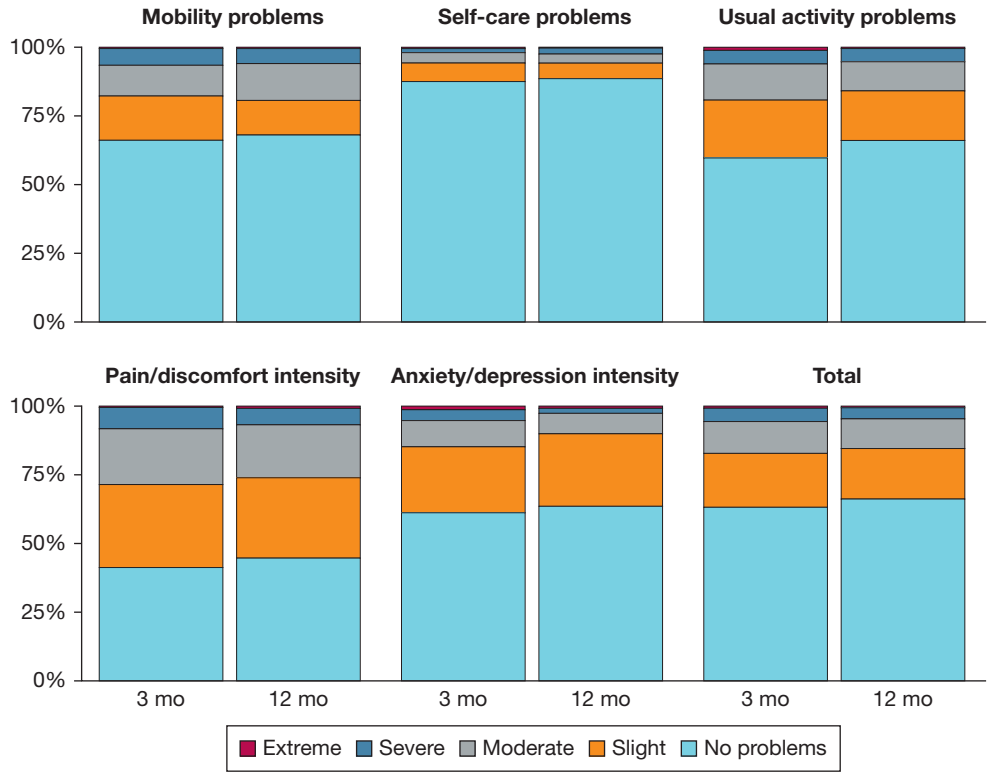

Figure 4 – *Distribution of generic health-related quality of life as assessed by the EuroQoL Group 5-Dimension 5-Level, dimension-specific and overall, at 3 and 12 months. Stacked bar plots showing the percentage of patients reporting no problems, slight problems, moderate problems, or severe problems in each one of the five dimensions of the EuroQoL Group 5-Dimension 5-Level health-related quality of life questionnaire and in the overall questionnaire at 3 months and 12 months.*

current study may be used by clinicians to better recognize those patients who may require additional testing and monitoring or changes in treatment. The use of quantitatively validated patient-reported outcomes as effectiveness end points in clinical trials is now recommended by both the US Food and Drug Administration[29] and the European Agency for the Evaluation of Medicinal Products.[30]

The current analysis has limitations. FOCUS is a prospective cohort study of patients with PE. Because we did not include a control study population without PE, we cannot draw conclusions on an independent association of PE with QoL; our findings are rather meant to provide estimates of the temporal course of QoL specific for this patient population. Because not all patients completed the PEmb-QoL questionnaires at both visits, selection bias against older patients and those experiencing chronic diseases cannot be excluded. However, < 25% of the patients in the current study were excluded from analysis because of missing questionnaire responses, and the rate of chronic disease in the remaining patients was similar to that reported in previous prospective studies of consecutive patients with PE.[31] Lastly, the racial and ethnic composition of the FOCUS cohort was relatively homogeneous. Care should be taken in generalizing our findings to more ethnically diverse populations.

Interpretation

In a large cohort of survivors among unselected patients treated for acute PE, both disease-specific and generic health-related QoL, as assessed by validated tools, improved between 3 and 12 months following acute PE in all their dimensions. Female sex, higher BMI, and preexisting chronic cardiopulmonary disease were associated with worse disease-specific QoL at both 3 and 12 months. Over time, the association with BMI became weaker, and QoL declined in older patients and those with a history of VTE. Our data may be relevant in the context of a more comprehensive and holistic evaluation of patients recovering from acute PE.

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